

REMARKS

A. Status of the Claims

Claims 1-7 were pending at the issuance of the instant Office Action mailed on October 19, 2007. Claims 1-7 are rejected in the instant Office Action. No claims are amended, added, or canceled herein. Applicants thank the Examiner for the previous consideration of our submissions.

B. Rejections under 35 U.S.C. § 103(a)

Claims 1-7 stand rejected under 35 U.S.C. 103 as being obvious over Malfroy-Camine *et al.* (6,064,188) in view of LaHaye *et al.* (5,075,116), Crapo *et al.* (5,994,339), Campbell *et al.* (6,177,419), and Winkler *et al.* (Molecular Vision 1999). The Action indicates that these references were cited for the following reasons: Malfroy-Camine *et al.* is said to teach the antioxidant and superoxide dismutase activity of the claimed compounds; LaHaye *et al.* is said to teach the use of free radical scavengers and antioxidants for treating diseases such as macular degeneration; Campbell *et al.* is said to teach that injection is a routine route of ophthalmic administration; Crapo *et al.* is said to teach that compounds having superoxide dismutase activity have previously been used for the treatment of AMD; and Winkler *et al.* is said to teach that there is a correlation between oxidation and macular degeneration and the effect of superoxide dismutase in preventing oxidative damage.

The Action asserts that one of skill in the art would have been motivated to combine the teachings of these references, because one of them teaches that the claimed compounds have superoxide dismutase activity, and the others allegedly relate to the use of superoxide dismutase compounds for the treatment of macular degeneration. As stated in MPEP §2143 (G):

The rationale to support a conclusion that the claim would have been obvious is that “a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success.”

Applicants submit that a person of ordinary skill in the art would not have been motivated to use the claimed compounds to treat persons suffering from the exudative and non-exudative forms of AMD, diabetic retinopathy, which includes proliferative diabetic retinopathy, or retinal edema based on the above references. Specifically, one of skill in the

art would not have been motivated by the teaching of Crapo *et al.* simply because Crapo *et al.* teach that oxidant scavengers may be useful for treating macular degeneration, and because both the claimed compounds and the Crapo compounds have SOD activity. In spite of the Actions' repeated argument that the compounds of Crapo *et al.* are structurally similar to the claimed compounds, Applicants again point out that the claimed compounds are salen-Mn compounds. Crapo *et al.* do not teach or suggest that salen-Mn compounds may be useful in place of the structurally different SOD mimetics they disclose. In addition, one of skill in the art would not have been motivated to use the claimed salen-Mn compounds in view of the teachings in Crapo *et al.* simply because the Crapo compounds and the claimed compounds both have SOD activity, because, as discussed below, there was no expectation of success with respect to the use of SOD compounds for treating the claimed disorders, even in view of the teachings of Winkler *et al.* and LaHaye *et al.*

The Action asserts that Winkler *et al.* is a valid reference for an obviousness rejection, because it suggests that there is a correlation between oxidation and macular degeneration and the use of superoxide dismutase in preventing oxidative damage caused by macular degeneration. As stated in MPEP §2143.02 (II):

The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. Where the teaching of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another.

As pointed out in Applicants' Response filed August 1, 2007, although Winkler *et al.* suggest, without any data to support the suggestion, that superoxide dismutase may be useful in protecting against macular degeneration, there were teachings in the art at the time the instant application was filed that conflicted with the teaching in Winkler *et al.* The instant Action does not address Applicants' discussion of the art that conflicted with Winkler, which must be considered pursuant to MPEP §2143, as pointed out above.

As discussed in Applicants' Response filed August 1, 2007, De La Paz *et al.* (1996, *Br. J. of Ophthalmology* 80:445-450; copy attached) and Delcourt *et al.* (1999, *Ophthalmology* 106:215-221; copy attached) both involve research studies in which blood samples were taken from a group of participants in order to statistically analyze the levels of superoxide dismutase activity in comparison to the severity of AMD. The De La Paz study included 66 participants, 54 of whom showed varying levels of severity of aging

maculopathy. The paper concluded based on multiple regression analysis and ordinal logistic regression analysis that there is no significant association between disease severity of AMD and superoxide dismutase activity. The Delcourt study included 2,156 participants for its analysis of AMD and antioxidant enzymes, 38 of whom had late AMD. The paper concluded, based on similar statistical analyses, that high levels of erythrocyte superoxide dismutase activity were not associated with late AMD and early signs of AMD.

While both De La Paz and Delcourt acknowledged that oxidative mechanisms may play a role in the development of AMD, each provided statistical data that higher levels of the enzyme do not correspond to the severity of AMD. Neither of these references showed or suggested that superoxide dismutase could be used to treat macular degeneration. In fact, these papers seemed to suggest that an increase in the amount of the enzyme would have no effect, because there is no association between the severity of AMD and the amount of superoxide dismutase activity. Thus, these papers appear to teach away from the use of superoxide dismutase for treating macular degeneration. Winkler *et al.* do not provide or discuss any data to refute the data or conclusions of De La Paz *et al.* or Delcourt *et al.* Consequently, one of skill in the art would not have been motivated to use compounds with superoxide dismutase activity for treating macular degeneration, since there would have been no reasonable expectation that the use of such compounds for that purpose would be successful based on the studies discussed in De La Paz *et al.* and Delcourt *et al.*

Further, no one of skill in the art would have been motivated to use the claimed compounds in the methods of the invention based on the teaching of LaHaye *et al.* The Action asserts that LaHaye *et al.* teach that free radical scavengers and antioxidants can be used to treat macular degeneration. Such teaching in LaHaye *et al.* relates to the use of small vitamin antioxidants, an amino acid (L-cysteine), and cofactors (such as zinc, copper, selenium, and manganese) for metalloenzymes, not to superoxide dismutase mimics. Thus, the teaching in LaHaye *et al.* would not have motivated one of skill in the art to use superoxide dismutase compounds for treating macular degeneration, diabetic retinopathy, or retinal edema.

The Action indicates that Campbell *et al.* was cited simply to demonstrate that injection is a routine route of ophthalmic delivery. Applicants point out, however, that Campbell *et al.* teach ophthalmic administration of bipyridine manganese complexes, and that the compounds taught by Campbell *et al.* are not the compounds of the instant claims.

Furthermore, nothing taught by Campbell *et al.* would have motivated one of skill in the art to use the claimed compounds to treat macular degeneration, diabetic retinopathy, or retinal edema. The mere teaching that bipyridine manganese complexes can be administered to the eye does not make it obvious to treat macular degeneration, diabetic retinopathy, or retinal edema with unrelated compounds. In addition, as discussed above, the teachings of LaHaye *et al.*, Crapo *et al.*, and Winkler *et al.* would not have motivated one of skill in the art to use superoxide dismutase compounds to treat macular degeneration, diabetic retinopathy, or retinal edema. Thus, there is no reason to believe that adding the teaching of Campbell *et al.* to the teachings of those references would have suggested the instant invention.

In conclusion, the combination of teachings of the cited references does not teach or suggest the use of the claimed compounds for treating macular degeneration, diabetic retinopathy, or retinal edema, and there would have been no reasonable expectation of success with respect to such use in view of the totality of the art at the time the instant application was filed.

In light of the foregoing arguments, Applicants respectfully request that the obviousness rejection be withdrawn.

C. Conclusion

This is submitted to be a complete response to the outstanding Action. The Examiner is invited to contact the undersigned attorney at (817) 615-5330 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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